PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference LEA36608-WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/001423	International filing date *(day/month/year)* 13 February 2004 (13.02.2004)	Priority date *(day/month/year)* 26 February 2003 (26.02.2003)]
International Patent Classification (IPC) or national classification and IPC [7] G01N 33/88, C12Q 1/68, A61K 39/00, 38/00		
Applicant BAYER HEALTHCARE AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 26 August 2005 (26.08.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ellen Moyse
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/001423	13.02.2004	26.02.2003

International Patent Classification (IPC) or both national classification and IPC
G01N33/88, C12Q1/68, A61K39/00, A61K38/00

Applicant
BAYER HEALTHCARE AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/001423

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-21,24-26 (in part), 22,23 (fully)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-21,24-26 (in part), 22,23 (fully) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-21,24-26 (in part), 22,23 (fully) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 26 (in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-26 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21,24-26 (partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21,24-26 (partially)
Industrial applicability (IA)	Yes:	Claims	1-21,24,25 (partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 19-21,24-26 relate to pharmaceutical compositions, their production and their use defined by reference to a desirable characteristic or property, namely binding to or regulating the activity of a GPCR prostaglandin E2 EP3 II polypeptide. The claims cover all pharmaceutical compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such pharmaceutical compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the pharmaceutical compositions by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, namely those parts relating to the examples (antisense oligonucleotide, antibody). Consequently the examination shall only evaluate these compounds with regard to novelty, inventive step and industrial applicability.

Present claims 1-26 relate to an extremely large number of possible diseases. In fact, the terms used to identify the different diseases are so broad and vague that a lack of clarity (and/or conciseness) within the meaning of Art. 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the relationship between GPCR prostaglandin E2 EP3 II and specific diseases/tissues, based on Table 1. The present examination will only take into account cardiovascular diseases (for reasons precised under item IV). Serious doubts are present with regard to the technical validity of the present invention in as far as cardiovascular diseases are concerned: From the data of Table 1, page 105, lines 15-29, it is not clear which data are supposed to have a significant correlation with a cardiovascular disease. The only difference in expression between a diseased cardiovascular

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tissue and its normal counterpart is found in the aorta. The examiner is even of the opinion that the small difference in expression levels of mRNA of GPCR prostaglandin E2 EP3 II between sclerotic aorta and normal aorta (page 58, lines 11-15), does not convincingly allow for an unambiguous diagnosis of atherosclerosis. Therefore in as far cardiovascular diseases are concerned the present application is not considered to provide an enabling disclosure allowing for a disease association with GPCR prostaglandin E2 EP3 II. The claims 1-26 therefore do not fulfill the requirements of Articles 5 PCT (disclosure) and 6 PCT (support) in as far cardiovascular diseases are concerned.

Furthermore claims 22 and 23 are also flawed with respect to Articles 5 PCT (disclosure) and 6 PCT (support), because there are neither experimental results nor teachings as to why the administration of a pharmaceutical composition comprising GPCR prostaglandin E2 EP3 II polypeptides or polynucleotides could have a therapeutical function in a patient. The technical validity of these claims is so seriously compromised, that no opinion will be given as to novelty, inventive step and industrial applicability.

Claim 26 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

According to the description the problem to be solved in the present application relates to novel disease associations of the G-Protein coupled receptor prostaglandin E2 EP3 II polypeptides/polynucleotides (page 5, lines 1-15). The single general concept which can be identified as a priori linking the various claimed inventions is the notion that the G-Protein coupled receptor prostaglandin E2 EP3 II is (potentially) associated with diseases.

WO02061087 (hereinafter referred to as D1; relevant passages cited in the ISR) and WO9500552 (hereinafter referred to as D2; relevant passages cited in the ISR) disclose a G-Protein coupled receptor prostaglandin E2 EP3 II and

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association between G-Protein coupled receptor prostaglandin E2 EP3 II and various disorders (Note that the G-Protein coupled receptor prostaglandin E2 EP3 21 polypeptide of WO9500552 is 99,7% identical to the G-Protein coupled receptor prostaglandin E2 EP3 II of the present application and therefore qualifies as a G-Protein coupled receptor prostaglandin E2 EP3 II). D1 and D2 therefore establish a relationship between the G-Protein coupled receptor prostaglandin E2 EP3 II and several diseases.

In the light of D1 and D2, each document if taken alone, the above identified single general concept is neither novel nor inventive and can thus not be the single general concept as required by Rule 13.1 PCT. The present application is therefore considered not to fulfil the requirement of unity as laid down in Rule 13.1 PCT.

The objective problem is then to provide further disease associations for the G-Protein coupled receptor prostaglandin E2 EP3 II . Each of the different disease-associations found is then a separate solution to this problem not sharing a special technical feature in the sense of Rule 13.2 PCT.

Consequently the groups of inventions are split up as follows:
The G-Protein coupled receptor prostaglandin E2 EP3 II in methods for screening for therapeutic agents useful in the treatment of diseases, in methods of diagnosis of said diseases, pharmaceutical compositions containing therapeutic agents for the treatment of said diseases, their production and their use, in which the diseases are:
1) cardiovascular diseases,
2) urological diseases,
3) metabolic diseases,
4) endocrinological diseases,
5) gastrointestinal diseases,
6) cancer and
7) dermatological diseases.

No other technical features could be identified that form a technical relationship among each of the separate inventions claimed and which could be considered as a special technical feature within the meaning of Rule 13.2 PCT. The

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invention first mentioned in the claims (involving cardiovascular diseases) has been searched.

Since the applicant has not paid further fees, only the invention first mentioned in the claims (involving cardiovascular diseases) has been examined.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/061087 A (ROUSH CHRISTINE L ; BROWN JOSEPH P (US); BURMER GLENNA C (US); LIFESPA) 8 August 2002 (2002-08-08)

D2: WO 95/00552 A (MERCK FROSST CANADA INC ; RUSHMORE THOMAS H (CA); ADAM MOHAMMED (CA);) 5 January 1995 (1995-01-05)

D3: PAUL B Z S ET AL: BRITISH JOURNAL OF HAEMATOLOGY, vol. 102, no. 5, September 1998 (1998-09), pages 1204-1211.

D4: WO 03/064471 A (DECODE GENETICS EHF ; GUDMUNDSSON GUDMUNDUR (IS)) 7 August 2003 (2003-08-07)

1 The present application meets the criteria of Article 33(2) PCT, because the subject-matter of claims 1-21 and 24-26 is new.

1.1 The document **D1** is regarded as being the closest prior art to the subject-matter of claims 1-21 and 24-26, and shows (the references in parentheses applying to this document):

D1 discloses the notion that several GPCRs among which GPCR prostaglandin E2 EP3 II (Seq ID 293) are associated with diseases among which cardiovascular diseases such as atherosclerosis, cardiomyopathy and circadian rhythm disorders (page 6, line 25-page 7, line 32. D1 specifically states that the antibodies against the GPCRs can be used to diagnose a variety of diseases and disorders. However, D1 does not unambiguously associate GPCR prostaglandin E2 EP3 II with cardiovascular diseases, which is an essential feature of claims 1-21 and

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24-26 for the invention to be examined as mentioned under item IV. Therefore in the light of D1, claims 1-21 and 24-26 can be considered to be new.

1.2 With regard to claims 1-21 and 24-26, D2 represents a close state of the art and discloses binding and activity assays involving GPCR Prostaglandin EP3 21 (example 6), the polypeptide of which is 99,7% identical GPCR prostaglandin E2 EP3 II and therefore qualifies as a GPCR prostaglandin E2 EP3 II (see description of the present application page 9, lines 12-24). D2 also suggests screening methods for modulators of isoforms of GPCR Prostaglandin EP3 (claim 8) and suggests that these modulators can be useful in treating disease states involving the EP3 receptor activity (e.g. glaucoma, tumour states etc. (page 16, lines 1-18)). The subject matter of claims 1-26 differs from D2 in that such assays are employed as screening assays for the identification of therapeutic agents useful in the treatment of cardiovascular diseases.

Therefore the subject matter of claims 1-21 and 24-26 is new in the sense of Article 33(2) PCT.

2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-26 does not involve an inventive step in the sense of Article 33(3) PCT.

2.2 With regard to claims 1-17 the documents **D1** can be regarded as being closest prior art to the subject-matter of claims 1-17 which differs therefrom as mentioned under item 1.1.

The problem to be solved by the present invention may therefore be regarded as the provision of screening assays for the identification of therapeutic agents useful in the treatment of cardiovascular diseases.

The solution proposed in independent claims 1-17 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

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Since D1 discloses GPCR prostaglandin E2 EP3 II (Seq ID 293) among the GPCRs which are suggested to be associated with diseases (among which cardiovascular diseases such as atherosclerosis, cardiomyopathy and circadian rhythm disorders (page 6, line 25-page 7, line 32)), D1 actually gives enough incentive to a person skilled in the art to test whether GPCR prostaglandin E2 EP3 II is de facto associated with these diseases and will arrive at the conclusion of the present application. Then the only problem left is the trivial provision of screening tests for identifying modulators of the receptor, which is a standard practice for a person skilled in the art (e.g. claim 8 of D2).

2.2 The same type of reasoning applies mutatis mutandis to independent claim 18, knowing that D1 suggests the use of antibodies against GPCR prostaglandin E2 EP3 II to diagnose a variety of diseases and disorders.

2.3 With regard to independent claims 19-21 and 24-26, the problem to be solved by the present invention may be regarded as the provision of pharmaceutical composition for the treatment of cardiovascular diseases. The solution proposed in independent claims 19-21 and 24-26 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
As mentioned under 2.1 D1 actually gives enough incentive to a person skilled in the art to test whether GPCR prostaglandin E2 EP3 II is de facto associated with these diseases. Then the only problem left is the trivial provision of modulators of the receptor. It is well known that antibodies against a receptor or antisense oligonucleotides against the DNA of this receptor are standard modulators for such a receptor. D1 for instance already suggests antibody-based therapeutics (page 10, lines 22-26). Therefore there will be no technical obstacle for a person skilled in the art to provide pharmaceutical composition comprising these.

3 Claims 1-21,24 and 25 fulfill the requirements of Article 33(4) PCT and are considered to be industrially applicable.

3.1 For the assessment of the present claims 26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting

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States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
It is noteworthy that although claim 26 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.